

**DECLARATION OF DR. BRUCE WHITELAW**

I, Christopher Bruce Alexander Whitelaw, declare as follows:

1. I am an inventor of the invention claimed in US Patent Application No. 10/522,536, derived from International Patent Application No. PCT/GB2003/003192, filed on 25 July 2003.
2. I obtained an honours degree in Biology in 1982 from the University of Edinburgh, UK and a PhD on the analysis of the transcriptional control domains of the human *c-myc* proto-oncogene in 1986 from the University of Glasgow, UK. I have been the Head of the Division of Developmental Biology at the Roslin Institute, Edinburgh, UK since 2005. I am currently the Editor-in-Chief of the publication Transgenic Research and the co-director of the Scottish Network of Excellence for the Development of Novel Technologies to Fight Viral Disease in Farm Animals. I have authored or co-authored a large number of papers regarding cloning techniques and transgenic animals. My curriculum vitae including a list of these publications is enclosed herewith as Appendix A.
3. Currently, I am Head of the Division of Developmental Biology at the Roslin Institute, Edinburgh, UK.
4. I am familiar with the above-referenced patent application and the Office Action dated 14 December 2007. I understand that objections have been raised under 35 USC §112 and that the Examiner considers that the claims do not comply with the written description requirement or the enablement requirement. I understand that the claims that have been examined are directed to a method of detecting a gene activation event *in vivo* by assaying a transgenic non-human animal whose cells express a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of the Cyp11a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID NO. 1, wherein the animal is subjected to a gene activation event of toxicologically induced stress, and a method of screening for, or monitoring of toxicologically induced stress by using said transgenic non-human animal. I understand that the claims have now been limited to transgenic rodents.

5. The Examples of the present application provide sufficient information to a person of skill in the art to produce a transgenic rodent as now claimed for use in the present invention.

6. In particular, Example 11 gives guidance regarding the expression of epitope tagged lipocalin reporter proteins in transgenic animals. Example 11 teaches that transgenic animals can be generated using one of several standard methods in the art including pronuclear injection, blastocyst injection of transfected cells or using viral vectors. These methods were well known in the art at the priority date of the present invention and a skilled person would readily be able to carry out these methods using their knowledge and the teachings of the scientific papers referred to on page 48, lines 15 to 19 of the present application.

7. Example 11 also gives specific guidance as to how to product transgenes containing the Cyp1a1 promoter sequence driving expression of myc epitope tagged BLG reporter, as described on page 48, line 25 to page 49, line 7.

8. The present application also gives guidance as to how to identify positive transgenic animals by analysis of DNA. Page 49, lines 9 to 15 of the present application also demonstrates how to detect and screen for a gene activation event of toxicologically induced stress. In particular, page 49, lines 10 to 15 specify that transgenic animals are exposed to stress, for example by drug administration, and blood and urine samples are collected over time. Samples collected pre- and post-insult are analysed for the presence of the tagged lipocalin by methods including Western blot and ELISA. Depending on the specific insult or inducing agent an increase or decrease in reporter activity are detected.

9. The Cyp1a1 promoter is also well described and characterised in the art, for example in WO 97/23635.

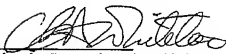
10. It is thus my opinion that one skilled in this field would be able to put the invention into practice using the disclosure of the present application and would believe that the inventors had possession of the invention now claimed.

Declaration of Dr Bruce Whitelaw

US Patent Application No. 10/522,536

Date 8<sup>th</sup> May 2008

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Christopher Bruce Alexander Whitelaw.

## Appendix A

### Curriculum Vitae

Bruce Whitelaw

1<sup>st</sup> March 2008

I am Head of Division at: The Roslin Institute and Royal (Dick) School of Veterinary Studies  
Division of Developmental Biology  
University of Edinburgh  
Roslin, Midlothian  
EH25-9PS  
Scotland, UK

#### Education

1982	BSc (2.1)	University of Edinburgh	Biology (Virology elective)
1987	PhD	University of Glasgow	(Beatson Institute)

Thesis "An analysis of the transcriptional control domains of the human *c-myc* proto-oncogene" supervised by Neil Wilkie.

#### Positions

2005 – present	Head of Division
2001 – present	Member of Roslin Animal Ethics Committee
2005 – present	Member of Institute Executive Committee
2006 – present	Member of Roslin Research Ethics Committee
2007 – present	Member of Institute Science Management Group
2007 – present	Member of Institute Finance and Business Committee
2007 – present	Chair of Institute Search Committee
2007 – present	Member of Roslin Institute Postgraduate Student Committee
2007 – present	Member of Easter Bush Research Consortium Executive Committee
2007 – present	Member EBRC Building Steering Group

#### External:

1999 – present	Editor <i>Transgenic Research</i>
2006 – present	Member OIE Ad hoc Group on Biotechnology
2007 – present	Co-director Scottish Network of Excellence for the Development of Novel Technologies to Fight Viral Disease in Farm Animals
2007 – present	Member of Scientific Council of ImmunoGenes Ltd (Budapest)

#### Previous positions:

2004 – 2005	Genetic Modification Programme Coordinator at Roslin Institute
2000 – 2003	Head of Small Animal Unit (10 staff)
1994 – 2005	Principal Investigator at Roslin Institute
1994 – 2005	Member of Roslin Institute's Genetic Modification Safety Committee
1994 – 2000	Institute Biological Safety Officer
1994 – 2000	Member of Roslin Institute's Health and Safety Committee
1986 – 1994	Research Scientist at Roslin Institute (formerly IAPGR, formerly ABRO)

#### External:

2001 – 2006	Member EU COST B20 Action Management Committee
2000 – 2004	Invited lecturer for Genetics and Molecular Biology (Science Faculty) Honours students, University of Edinburgh
2000 – 2003	Honorary Research Fellow of Hannah Research Institute (Ayr, UK)
2000 – 2003	Member of HSE's Advisory Committee of Genetic Modification (ACGM)

### **Additional Details on Committees/Groups**

- OIE Ad hoc Group on Biotechnology – an interdisciplinary international group developing guidelines for research on vaccines in animal health application of nanoscience/nanotechnology as it relates to animal health and animal health risks related to somatic cell nuclear transfer.
- Contributed to the build project for The Roslin Institute (temporarily called the EBRC) through membership of Building Steering Group and Architect Users Group.

### *Previous:*

- COST B20 Action Management Committee – UK representative on European funded Cooperation in the field of Science and Technical Research action “Mammary gland development, function and cancer”.
- Advisory Committee of Genetic Modification (ACGM) – BBSRC proposed member on Health & Safety Executive’s advisory committee providing technical and scientific advice to the UK Competent Authorities on all aspects of the human and environmental risks of the contained use of genetically modified organisms (GMOs).

### **Visiting Groups**

- Review of University of Veterinary Studies (VUW), Vienna (Vienna, 2008).
- Review of Europäische Akademie study “Pharming: Genetically modified plants and animals as future production site of pharmaceuticals” (Berlin, 2007).
- Review of Xenotransplantation Research Unit led by Prof Bruno Reichart on behalf of the Deutsche Forschungsgemeinschaft (Munich, 2007).
- Review of pre-proposals for Graduate Schools and Centres of Excellence in Biomedical Sciences on behalf of the Deutsche Forschungsgemeinschaft (DFG), the main funding agency for basic research in Germany (Frankfurt, 2006).
- Review of research infrastructure on behalf of the Higher Education Authority (HEA) of Ireland to forge a top level Roadmap for Investment in Research Infrastructure in Ireland (Trinity College Dublin/University College Dublin/NUI Galway, 2006).

### **Additional Information**

- BBSRC Institute Career Path Fellowship interview panel (2008)
- Invited participant in Technology Strategy Board BioScience Roadmap Workshop (2008)
- Reviewer for Science Foundation Ireland Equipment Call (October 2007)
- Invited participate at Genesis Faraday Workshop on genetics of livestock emissions (Edinburgh, 2007).
- European Science Foundation peer reviewer (2007-2008).
- Reviewed selection of topics for future priority setting of life sciences in Austria for Austrian Council for Research and Technology Development (2006).
- Reviewed Transitional Funding with regard to Hannah Research Institute staff for SEERAD (2006).
- Invited participant at EC RETHINK project (2006-2007).
- Presented at British Council Café Scientifique, Paris, (2006).
- Invited expert at EC Cloning in Public Project (2005, 2006).
- Scientific Expert for the EC COST Mammary Gland Biology Network on trips to Italy, France and Hungary (1997-2002).
- Invited participant at ICSU workshop on Risk/Benefit Assessment of GM Foods (Paris, 2001).
- Invited participant at EC Task Group Workshop on Public Perception of Transgenic Animals (Helsinki, 2000).
- Member of International Society of Transgenic Technologies (ISTT).
- Regularly review grants for BBSRC, MRC, EC and Wellcome Trust.
- Nominated to Cartagena Protocol on Biosafety roster of experts.
- PhD thesis External Examiner for Universities of Edinburgh (UK), Imperial College London (UK), Paris and Limoges (France), Barcelona (Spain) and Waikato (New Zealand).
- Received financial support from BBSRC, SHEFC, IACR, BCC, Breakthrough Trust, EC FWIV/FWV/FWVI, ESTO, Genesis Faraday, Rainbow Fund and British Council; plus commercially funded projects with Sygen International and CXR Biosciences.

## Students Supervised

### PhD thesis:

- 1999 Simon A. Boa "Nucleosome organisation over the ovine  $\beta$ -lactoglobulin gene".  
2002 Margaret L. Opsahl "Variegated transgene expression in mice".  
2004 Gillian H. Little "Stat5 binding to chromatin".  
2004 Chris Palgrave "African Swine Fever Virus pathogenesis: comparative analysis of immunoregulatory genes in domestic and wild pigs".  
2006 Douglas B. Vasey "p21 expression in the mouse".  
2006 Ravikumar Manikam "Myostatin expression in the mouse mammary gland".  
2007 Rachel Young "Oxidative stress reporter genes".

### MSc thesis:

- 2004 Pali Verma "Modulation of immune system by down regulation of TNF receptors I, II and p65 gene expression by RNA interference".

## Meetings/Seminars

### Organised:

- COST 825 Working Group on Mammary Bioreactors (Roslin, 2000)
- ESF Workshop "Genetic Models of Disease Resistance on Transgenic Livestock" (Edinburgh, 2007)

### Co-organised:

- Royal Society of Edinburgh workshop on Mammary Gland Biology (Edinburgh, 1992)
- First International Workshop on Mammary Gland Biotechnology (Budapest, 1997)
- Second International Workshop on Mammary Gland Biotechnology (Budapest, 2001)

### Session chair:

- COST 825 Mammary Gland Biology Symposium (Tours, 1999)
- Second International Workshop on Mammary Gland Biotechnology (Budapest, 2001)
- Transgenic Animal Research Conference VI (Lake Tahoe, 2007)
- *International Conference on Biotechnology (2008)*

I have given 42 seminars within Europe, Japan and USA, and 26 seminars within the UK; most recently

- "Making transgenic animals with lentiviral vectors", Institute of Comparative Medicine, University of Glasgow, 7<sup>th</sup> February 2007
- "The many ways to make transgenic animals", RIVAGE EU Marie-Curie EU project, INRA, Jouy-en-Josas, 7<sup>th</sup> June 2007
- "Cloning and Genetics – what Roslin Institute does best", Ribblesdale Farmers Club, 12<sup>th</sup> December 2007

### Invited seminars:

- "Production of transgenic farm animals by viral vector mediated gene transfer", International Congress on Animal Reproduction, Budapest, 13<sup>th</sup>-17<sup>th</sup> July 2008.
- International Conference on Biotechnology, Dalian China, 12<sup>th</sup>-17<sup>th</sup> October 2008.
- Congress Biotechnology, Havana Cuba, 30<sup>th</sup> November - December 2008.

## PUBLICATIONS

- Lang JC, Whitelaw B, Talbot S and Wilkie NM (1988) Transcriptional regulation of human c-myc gene. *Br J Cancer*, 58, 62-66.
- Clark AJ, Bessos H, Bishop JO, Brown P, Harris S, Lathe R, McClenaghan M, Prowse C, Simons JP, Whitelaw CBA and Wilmot I (1989) Expression of human anti-hemophilic factor IX in the milk transgenic sheep. *Bio/Tech* 7, 487-492.
- Clark AJ, Ali S, Archibald AL, Bessos H, Brown P, Harris S, McClenaghan M, Prowse C, Simons JP, Whitelaw CBA and Wilmot, I (1989) The molecular manipulation of milk composition. *Genome* 31, 950-955.
- Whitelaw CBA and Clark AJ (1989) Animal bioreactors. *AgBiotech News and Information* 1, 701-705.
- Wilmot I, Archibald AL, Harris S, McClenaghan M, Simons JP, Whitelaw CBA and Clark AJ (1990) Methods of gene transfer and their potential use to modify milk composition. *Theriogenol* 33, 113-123.
- Whitelaw CBA, Archibald AL, McClenaghan M, Harris S, Simons JP, Watson CJ, Wilmot I and Clark AJ (1990) Expression of  $\beta$ -lactoglobulin and hybrid transgenes in the mammary gland. *Proc Biotech USA*, pp. 130-136.
- Clark AJ, Archibald AL, McClenaghan M, Simons JP, Whitelaw CBA and Wilmot I (1990) The germline manipulation of livestock: progress during the past five years. *Proc NZ Soc Animal Prod* 50, 167-179.
- Lang JC, Wilkie NM, Clark AM, Chudleigh A, Talbot S, Whitelaw B and Frame MC (1991) Regulatory domains within the P0 promoter of human c-myc. *Oncogene* 6, 2067-2075.
- Whitelaw CBA, Archibald AL, Harris S, McClenaghan M, Simons JP, Springbett A, Wallace R and Clark AJ (1990) Frequency of germline mosaicism in G0 transgenic mice. *Mouse Genome* 88, 114.
- Whitelaw CBA, Archibald AL, Harris S, McClenaghan M, Simons JP and Clark AJ (1991) Targeting expression to the mammary gland: intronic sequences can enhance the efficiency of gene expression in transgenic mice. *Transgenic Res* 1, 3-13.
- McClenaghan M, Archibald AL, Harris S, Simons JP, Whitelaw CBA, Wilmot I and Clark, AJ (1991) Production of human  $\alpha$ 1-antitrypsin in the milk of transgenic sheep and mice: targeting expression of cDNA sequences to the mammary gland. *Anim Biotech* 2, 161-176.
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- Springbett AJ, Burdon T, Yull FE and Whitelaw CBA (1993) Comment on mosaic nature of G0 transgenic mice. *Mouse Genome* 91, 113.
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36. Whitelaw CBA (1999) Toward designer milk. *Nat Biotech* 17, 135-136.
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66. Flint DJ, Boutinaud M, Tonner E, Wilde C, Hurley W, Accorsi PA, Kolb A, Whitelaw CBA, Beattie J and Allan GJ (2005) Insulin-like growth factor binding proteins initiate cell death and extracellular matrix remodelling in the mammary gland. *Dom Anim Endocrinol* 29, 274-282.
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69. Kolb AF and Whitelaw CBA (2006) Heavy chain toxicity in embryonic stem cells. *Mol Immunol* 43, 677-89.
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71. Gencheva M, Boa S, Fraser R, Simmen MW, Whitelaw CBA and Allan J (2006) In vitro and in vivo nucleosome positioning on the ovine beta-lactoglobulin gene are related. *J Mol Biol* 361, 216-230.
72. Ritchie WA, Neil C, King T and Whitelaw CBA (2007) Transgenic mice produced from low titre lentiviral vectors. *Transgenic Res* 16, 661-664.
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77. Strathdee D, Whitelaw CBA and Clark AJ (2008) Early embryonic  $\beta$ -actin expression is not sufficient for CpG-island maintenance. *J Biol Chem* 283, 11509-11515.
78. Rowe J, Welsh C, Pena RN, Wolf CR, Brown K and Whitelaw CBA (in press) Illuminating the role of CYP1A1 in skin. *J Invest Dermat*
79. Manickam R, Pena RN and Whitelaw CBA (in press) Mammary gland differentiation inversely correlates with GDF-8 expression. *Mol Reprod Dev.*

80. Ritchie WA, King T, Neil C, Carlisle A, Lillico S, McLachlan G and Whitelaw CBA (in press) Transgenic sheep designed for transplantation studies. *Mol Reprod Dev*
81. Nelson L, Anderson S, Archibald AL, Rhind S, Condie A, Lu Z, McIntyre N, Thompson J, Nenutil R, Vojtesek B, Whitelaw CBA, Little T and Hupp T (in press) an animal model to evaluate the function and regulation of actively evolving stress protein SEP53 in oesophageal bile damage response. *Cell Stress Chaperon*

#### **Patents**

1. Archibald AL, Clark AJ, Harris S, McClenaghan M, Simons JP and Whitelaw CBA (1989) A genetic construct of which protein-coding DNA comprises introns and is designed for protein production in transgenic animals. PCT/GB89/01343.
2. Whitelaw CBA, Clark AJ and Wolf CR (2003) Multi-reporter gene model for toxicological screening. PCT/GB2003/003192.
3. Clark AJ and Whitelaw CBA (2004) Disease resistant transgenic non-human animals. PCT/GB2004/002793.
4. Wolf CR, Whitelaw CBA, Clark AJ, Brown K and Temperley SM (2004) Excretable reporters. PCT/GB2004/004054.
5. Wolf CR, Whitelaw CBA, Clark AJ, Brown K. Detection of cellular stress.